



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Heikki HYOTY, et al

Serial No.: 10/009,016

Group No.: 1645

Filed: March 12, 2002

Examiner.: Mary Mosher

For: PREVENTION OF TYPE 1 DIABETES AND OTHER NON-POLIO
ENTEROVIRUS DISEASES

Attorney Docket No.: U 013757-2

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, Professor Heikki Hyoty, declare as follows:

1. I am a co-inventor of the invention described and claimed in the above application. My academic background and professional experience are as shown on my *curriculum vitae*, which is annexed hereto as Exhibit 1.
2. I make this declaration in support of the above application. I have firsthand knowledge of the trial described below, which was carried out under my supervision and control.

Summary of the OPV trial among children with increased genetic risk for type 1
diabetes

The protective effect of the proposed OPV vaccination regime was tested in children who were at increased genetic for type 1 diabetes. In this trial 64 children were immunized with OPV at early age according to the proposed immunization regime: Although 4 doses of OPV were given repeatedly to each

child at the age of 2 months, 3 months, 6 months and 12 months. In addition, 700 control children were immunized with inactivated poliovirus vaccine (IPV) at an older age (at the age of 6 months, 12 months and 24 months). The OPV immunizations were carried out by using a commercially available OPV vaccine according to the standard per os protocol (one dose included two drops of vaccine given directly to the mouth). Each dose included a mixture of the three poliovirus Sabin strains (poliovirus 1, 2 and 3) in the following concentrations (TCID₅₀): poliovirus 1: 10^6 ; poliovirus 2: 10^5 ; poliovirus 3: $10^{5.8}$. All immunized children carried HLA-genes, which increased their risk for type 1 diabetes, determined by the screening of the HLA-DQ alleles at birth. Recruited children carried the HLA-DQB1*302 risk allele but were negative for HLA-DQB1*0201, HLA-DQB1*0301 and HLA-DQB1*0602 alleles. All immunized children were followed from birth and serum samples were regularly taken at the age of 3 months, 6 months, 9 months, 12 months, 18 months, 24 months and then annually. The children were followed from birth for an average of 3.5 years in both groups.

The effect of OPV was analyzed by studying its effect on the appearance of beta-cell damaging autoimmune process. This process can be identified by the presence of autoantibodies in serum (islet-cell autoantibodies, insulin autoantibodies, GAD65-autoantibodies and IA-2 autoantibodies) and leads to clinical type 1 diabetes after a lag period ranging from some weeks/months to

several years. These autoantibodies were measured from serum samples from all children in the OPV-immunized and in the control group. OPV-immunized children turned positive for these autoantibodies less frequently than control children. Altogether 4.5% of the OPV-immunized children turned positive for at least one of these autoantibodies during the observation compared to 10.0% of control children ($p=0.05$). The results show that the proposed OPV immunization can decrease the risk of autoimmune beta-cell damaging process in genetically susceptible individuals.

3. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity or the application of any patent issued thereon.

Date: JANUARY 3, 2006



Professor Heikki Hyoty

CURRICULUM VITAE

FULL NAME

HYÖTY, Heikki Antero

DATE AND PLACE OF BIRTH

June 9, 1959, Tampere, Finland

CURRENT POSITION

Professor of Biomedicine and Virology, University of Tampere, Medical School, 2004-

EDUCATION AND TRAINING

- Graduated from Tampereen Lyseo co-educational School, Tampere, Finland 1978
- Matriculated in the medical faculty of the University of Tampere 1978
- Medical Doctor, graduated from medical school 1983
- State license for practicing medicine (General practice) 1985
- PhD (medical faculty of University of Tampere) 1989 (thesis defended 1988)
- Military service (second lieutenant) 1989
- Docent in virology, University of Tampere, 1994
- Docent in virology, University of Turku, 1996

PREVIOUS PROFESSIONAL APPOINTMENTS

Virology and immunology

- Senior Research Fellow, Academy of Finland, 1999-2004 (at the Department of Virology, University of Tampere, Medical School)
- Senior lecturer, University of Tampere, Medical School, Dep. of Virology, 1997-2002 (on leave 1999-2002)
- Research fellow, Department of Virology, University of Turku, 1995-97
- Research fellow, Department of Virology, University of Tampere, 1985-1995
- Part-time doctor at the Tampere University Hospital (Department of Clinical Microbiology, Virus laboratory), 1987-93
- Part-time doctor at the Diagnostic Service Laboratory for Clinical Virology at the University of Tampere, 1987-1993
- Part time specialist at the Microbiology branch of the Center for Laboratory Medicine at the University Hospital of Tampere 1997-

Other

- General practitioner 4 months in the Health Center of Tampere and 19 months (part time) in personnel health office 1984-85
- Physician 3 months in the local hospital of Valkeakoski (surgery, obstetry and gynaecology) 1984

RESEARCH AWARDS, HONORS AND MAJOR GRANTS

- Award of the Reserve Officers Training Corps Support Foundation 1989.
- Heine-Medin award of the European Society for Clinical Virology, 1994.
- Research award of Wilhelm and Else Stockmann Foundation, 1993 and 1994.
- Assistant of the year (awarded by the Medical Student Organization at the University of Tampere for teaching skills), 1994.
- Award for best article of the year by Finnish Medical Journal (Suomen Lääkärilehti) 1994.
- Post-doctoral fellowship grant by Juvenile Diabetes Research International, 1995.
- University of Tampere Medical School Award for distinguished scientific work, 1995.
- Mary Jane Kugel Award, Juvenile Diabetes Research Foundation International, 2005

EXHIBIT 1

MAJOR SOURCES OF FUNDING DURING THE LAST 5 YEARS

- International: Juvenile Diabetes Foundation International, European Union, EFSD/Novo Nordisk
- Finnish: The Academy of Finland, University Hospital of Tampere (EVO), Sohlberg's Foundation, Diabetes Research Foundation, Lehtikainen Foundation, The Tuberculosis Foundation of Tampere

MEMBERSHIP IN SCIENTIFIC SOCIETIES

- European Society for Clinical Virology (council member since 2000)
- European Association for the Study of Diabetes
- Juvenile Diabetes Foundation International
- Finnish Society for Immunology (member of board 1992-1999, secretary 1996-1997)
- Finnish Society for the Study of Diabetes (member of board 1995-2003, vice president 1996-2003)
- Reserve Officers Training Corps student organization (chairman 1989)
- Immunology of Diabetes Society
- Finnish Medical Association
- Finnish Medical Society Duodecim
- Finnish Society for Microbiology
- Finnish Society for Endocrinology

ADMINISTRATIVE DUTIES

- Member of the PhD Committee, University of Tampere, Medical School, 2004-
- Member of the Faculty Council of the Medical School, University of Tampere, 2004-
- Member of the Scientific Advisory Board of the Center for Laboratory Medicine, University Hospital of Tampere, 1999-
- Member of the R&D Committee of Molecular Genetics of the Center for Laboratory Medicine, University Hospital of Tampere, 2004-

OTHER ACADEMIC AND PROFESSIONAL MERITS AND ACTIVITIES

Supervisor for doctoral dissertations

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|-------------------------------------------------------------------------------------------------------------------------------------|------|
| -PhD Päivi Parkkonen: "Virus-induced autoimmunity in the pathogenesis of Type 1 diabetes, University of Tampere | 1993 |
| -MD, PhD Merja Hiltunen: "Seroepidemiological study of viral etiology in Insulin-Dependent Diabetes Mellitus, University of Tampere | 1996 |
| -MD, PhD Maria Lönnrot: "Enterovirus infections in the pathogenesis of Type 1 diabetes", University of Tampere | 1999 |
| -MD, PhD Sirpa Juhela: "Type 1 diabetes and cellular immune response to enteroviruses", University of Turku | 2000 |
| -MD, PhD Kimmo Salminen: "Enteroviruses in type 1 diabetes – evaluation in prospective Finnish Series", University of Turku | 2003 |
| -MD, PhD Karita Sadeharju: "Maternal and childhood enterovirus infections and the risk of beta-cell autoimmunity" | 2005 |
| -MD, PhD Hanna Viskari: "Enterovirus immunity and maternal enterovirus infections – connection to type 1 diabetes" | 2005 |

Examiner for doctoral dissertations

- | | |
|---------------------------------------------------------------------------------------------------------------------------------------|------|
| -MD Arno Hänninen: Mechanisms of lymphocyte accumulation in the endocrine pancreas in insulin-dependent diabetes, University of Turku | 1995 |
| -PhD Jorma Määttä: Experimental autoimmune encephalomyelitis of the BALB/c mouse, University of Turku | 1998 |
| -MD Ville Kytö: Fatal Myocarditis with special reference to viral etiology | 2005 |

and cardiomyocyte apoptosis, University of Turku

-MD Paula Kupila: "Aetiological Diagnosis of Acute Central Nervous System Infections in Adults - the role of PCR" 2005

Official opponent for doctoral dissertations

-MD Päivi Joki-Korpela: Molecular pathogenesis, antigenicity and epidemiology of human parechovirus 1, University of Turku 2001

-MD, PhD Richard Ellis: Naturally processed and presented peptide epitopes of Cosackievirus B4 P2C protein (King's and St Thomas' School of Medicine, University of London, UK) 2003

-MD, PhD Suvi Rasilainen: Cocksackievirus infections and oxidative stress as mediators of beta-cell damage, University of Helsinki 2004

Other scientific merits

-over 100 articles in scientific journals or books, several presentations in international congresses as an invited speaker.

-Referee of international scientific journals (e.g. Diabetologia, Diabetes Care, Diabetic Medicine, Journal of Infectious Diseases, Journal of Virology, Journal of Medical Virology, Journal of Clinical Virology, Vaccine)

-Reviewer of international scientific grant applications (e.g. member of Juvenile Diabetes Research Foundation Scientific Review Board 2003-2005, reviewer for Dutch Diabetes Foundation, Canadian Diabetes Association, Diabetes UK, Wellcome trust, Academy of Finland)

-Member of the steering committee of the JDRF Center for Prevention of Type 1 Diabetes Finland 1999-

-Co-ordinator of two EU-funded international multicenter studies:

- 1) Enterovirus infections in NIS/CCE countries and in EU, IC15-CT98-0316, years 1998- 2001.
- 2) Enterovirus Infections as a Risk Factor for Type 1 Diabetes, GLK2-CT-2001-01910, 2001- 2004 (www address <http://www.uta.fi/laitokset/laaket/VIRDIAB/>).

-Chairman of the Infectious Disease Committee of the international TEDDY Consortium (The Environmental Determinants of Diabetes in the Young; <http://www.teddystudy.org>), 2003-

-Member of scientific advisory committee of the TRIGR study (Trial to Reduce Insulin-Dependent Diabetes in the Genetically at Risk; <http://www.trigr.org>), 2002-

Teaching experience

-Courses and lectures for medical students at the University of Tampere (virology and immunology) in 1985-1995 and in 1997- (problem-based learning since 1997).

-Lectures for medical students at the University of Turku in 1995-1997.

-Published teaching material: Laboratory courses and workbooks for virology and for immunology for basic training of medical students at the University of Tampere.

-Several review articles in Finnish medical journals (Duodecim, Suomen Lääkärilehti).

Language skills

Finnish (mother tongue), Swedish, English and German.

Swedish is certificated as follows: Certificate awarded by a member of the State Language Examining Board in the practice of written and spoken language, Certificate for medical doctor-degree endorsed by the Council of the University of Tampere.

Social status

Married since 1983.

Two children, born in 1992 and 1998.

Curriculum completed July 17, 2005.
